

## REMARKS

### The Claim Amendments

Applicants have canceled claims 3, 7-9, and 12-19.

Applicants have added new claims 22-26 directed to a composition comprising a particular compound embodiment and methods of use therewith. Support for claims 22-26 is found in claims 19-21 and throughout the specification as filed.

Applicants have amended claims 1, 6, 10-11, and 20.

Applicants acknowledge that claims 20-21 are withdrawn from consideration because they are drawn to non-elected inventions. However, in case a linking claim is allowed and in order to expedite prosecution, applicants have amended claim 20 to depend from claims 1, 2, 4, 6 and 10-11.

Applicants have amended claim 1 to recite the compound species fludarabine. Support for this amendment is found in claims 13-16 as originally filed. Applicants have also amended claim 1 to recite particular compound embodiments for radicals R<sub>1</sub>, R<sub>2</sub>, R<sub>9</sub>, R<sub>10</sub>, and R<sub>11</sub>. Support for this amendment is found in claims 1, 4, 6 and 9 as originally filed.

Applicants have amended claims 10 and 11 to depict the structures of particular compound embodiments of the present invention. Support for these amendments is found in compound Table 1 in the specification at pages 14-45.

### The Rejections

#### 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-16 and 19 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically the Examiner asserts that the claims are very broad and inclusive of all apoptosis inducing anti-cancer agents that are used to treat cancers. The Examiner acknowledges that the working examples show fludarabine alone and in combination with the compositions of the present invention to treat cancer. However, the Examiner concludes that the scope of the present invention would require undue experimentation by one skilled in the art to practice the claimed invention.

As discussed above, applicants have canceled claims 3, 7-9 and 12-19 and

amended claim 1 to recite a composition comprising a single anti-cancer agent, fludarabine. Additionally, applicants have described an apoptosis assay used to evaluate the percent apoptotic effect of either fludarabine alone, compound 181 alone or a combination of both (e.g., see Example 1 at pages 58-59 of the specification and Figures 1 and 2). Therefore, one of skill in the art will readily appreciate that the composition of amended claim 1 is drawn to a scope that is readily ascertained and is commensurate in scope with applicants' disclosure and exemplification of anti-cancer activity. Furthermore, dependent claims 2, 4, 6, 10, 11 and 22 also incorporate this limitation. Accordingly, applicants respectfully request that the Examiner withdraw this rejection.

#### 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 10, 11 and 19 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically the Examiner asserts that claims 10, 11, and 19 are indefinite because they refer to compounds in a table. The Examiner has suggested inserting the structures of the compounds to overcome this rejection.

As discussed above, applicants have canceled claim 19 and amended claims 10 and 11 to depict the compound species claimed therein. Accordingly, applicants respectfully request that the Examiner withdraw this rejection.

#### 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-16, and 19 under 35 U.S.C. § 103(a) as being unpatentable over Montgomery (US 4,210,745) (hereinafter "Montgomery-1") or Montgomery (US 4,357,324) (hereinafter "Montgomery-2") in view of Stamos et al. (WO 00/56331) (hereinafter "Stamos"). According to the Examiner, Montgomery-1 teaches fludarabine and Montgomery-2 teaches fludarabine prodrugs both known to possess anticancer properties. The Examiner further contends that Stamos teaches compounds of the same structural formula (A) useful to treat cancers and tumors. The Examiner concludes that "one skilled in the art would have assumed the combination of two individual agents well-known as anticancer agents into a single composition would give an

additive effect in the absence of evidence to the contrary.” Applicants respectfully traverse in light of the above amendments and for the following reasons.

First, Montgomery-1, Montgomery-2, and Stamos do not teach or suggest the claimed combination of the present invention; namely the use of an IMPDH inhibitor of formula A in combination with an apoptosis inducing, anti-cancer and anti-metabolite agent such as fludarabine. Montgomery-1 teaches a procedure for preparing the anti-cancer agent fludarabine. Montgomery-2 teaches prodrug derivatives of fludarabine. Stamos teaches a genus of IMPDH inhibitors of formula A useful to treat cancers and tumors either alone or in combination with an additional anti-cancer agent. However, the specific combination of fludarabine with a compound of formula A is neither taught nor suggested by Montgomery-1, Montgomery-2, or Stamos. Therefore, one skilled in the art would not have been motivated nor would have found it obvious to make the combination of the present invention based on the species disclosed in Montgomery-1 and Montgomery-2 and the genus and combination disclosed in Stamos.

Second, the claimed combination of the present invention, namely an apoptosis inducing, anti-cancer agent (e.g., fludarabine) with an IMPDH inhibitor of formula A, imparts a surprising and unexpected synergistic rather than additive (emphasis added) increase in anti-cancer activity. Specifically, the claimed combination synergistically increases a cancer cells susceptibility to apoptosis and cell death. For instance, applicants have provided data (see, specification, Example 1, paragraphs [0065] to [0069] at pages 58-59) for the combination of representative compound number 181 either alone or in combination with fludarabine to evaluate the apoptotic effect (measured by percent apoptosis) on a Daudi cancer cell line. Figures 1 and 2 provide a graphical readout of the observed synergistic effects. Figure 1 shows the percent apoptosis against the concentration of compound 181 alone, fludarabine alone, and a combination of both agents. Therein, the combination of compound 181 and fludarabine results in a much greater percent apoptosis due to the synergy therebetween. Moreover, Figure 2 provides a graphical representation of the strong synergistic effect observed with the fludarabine/compound 181 combination. Therein, a CalcuSyn analysis of percent apoptosis (using the Guava Nexin assay to detect Annexin-Positive Daudi cells; see specification, Example 1, paragraph [0065]) shows a strongly synergistic effect at all three

doses tested, namely the ED50, ED75 and the ED90. Thus, the unexpected synergistic effect (as opposed to merely additive) observed for the claimed combination of the present invention renders it a non-obvious, patentable invention over Montgomery-1 or Montgomery-2 in view of Stamos.

In summary, the claimed combination of the present invention that provides a genus of compounds of formula A and an apoptosis inducing anti-cancer agent such as fludarabine is neither taught nor suggested by Montgomery-1, Montgomery-2, or Stamos. Furthermore, the unexpected synergistic effect and enhanced anti-cancer profile possessed by the claimed combination renders it non-obvious over Montgomery-1 or Montgomery-2 in view of Stamos. Accordingly, applicants respectfully request that the Examiner this § 103(a) rejection.

#### Non-statutory Double Patenting

The Examiner has rejected claims 1-11 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-11 of U.S. Patent No. 6,498,178 (hereinafter the “’178 patent”). Applicants respectfully traverse.

As discussed above, the claimed combination of the present invention provides an unexpected synergistic effect resulting in an enhanced anti-cancer profile. The ‘178 patent provides no teaching, suggestion or motivation to select the claimed combinations. Therefore, the present application is an unobvious, patentable invention over the ‘178 patent. Accordingly, applicants respectfully request that the Examiner withdraw this nonstatutory double patenting rejection.

#### Conclusion

Applicants respectfully request that the Examiner consider the foregoing remarks and allow the pending claims to pass to issue.

Respectfully submitted,

---

Michael C. Badia, Reg. No. 51,424  
Agent for Applicants  
c/o Vertex Pharmaceuticals Incorporated  
130 Waverly Street  
Cambridge, MA 02139-4242  
Tel.: (617)444-6467  
Fax.: (617)444-6483  
Customer No.: 27916